IN THE UNITED STATES PATENT OFFICE

In re Application of Thennati RAJAMANNAR *et al.*, "Process For the Preparation of [Citalopram]"	Serial No. 10/500,532 Filed 19 July 2004

DECLARATION

I, Thennati RAJAMANNAR, hereby swear as follows:

1. I am an inventor of record of the captioned patent application.

2. I attach a copy of my *curriculum vitae*. I believe that my background as shown there establishes that I am one of skill in the art of organic chemistry.

3. I have reviewed the Office Action (24 June 2005) and the art of record in this case, including Marco VILLA *et al.*, *Method For the Preparation of Pure Citalopram*, U.S. Letters Patent No. 6,455,710 B1 (24 Sept. 2002), and Hans PETERSEN *et al.*, *Crystalline Base of Citalopram*, PCT Patent Application No. WO 01/68627 A1 (20 September 2001).

4. The Office Action at page 5 requests Applicant to "demonstrate the criticality of the invention in view of the prior art." I here respectfully provide this demonstration.

5. The art of record teaches the existence of the drug Citalopram. *See e.g.*, PETERSEN at page 1, lines 3-5; VILLA at col. 1, lines 7-9. VILLA teaches that known Citalopram synthetic methods create unacceptable levels of an impurity called "desmethyl-citalopram." *See* VILLA at col. 1, lines 50-57 ("The process ... has been found to give the desmethyl-citalopram derivative in unacceptable amounts."). VILLA thus teaches a way to eliminate desmethyl citalopram by using a cyanide exchange process. *See id.* at col. 3, lines 46 *et seq*.

6. We have found, however, that VILLA's cyanide exchange process itself produces another impurity, 5-carboxamide –1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-phthalide, a

carboxamide derivative illustrated in our application at "Formula 4." *See* Specification at page 4, lines 1 *et seq*.

7. Neither VILLA nor PETERSEN mentions this contaminant. Neither VILLA nor PETERSEN appears to even recognize the existence of this contaminant, much less teach a way to eliminate it. To the contrary, VILLA teaches a cyanide exchange reaction which *creates* this contaminant. *See* Specification at page 4, lines 1 *et seq*.

8. Our invention provides a way to eliminate this contaminant. Our claimed invention differs from the art of record by including several elements not found in the art of record, to produce a result not achieved by the art of record.

9. Our claims require "presence of an iodide." *See* claim 1, element (a). In contrast, neither VILLA nor PETERSEN mentions adding iodide to the reaction mixture. Furthermore, one of skill in the art would not read these references to suggest adding iodide.

10. Our claims require use of "phosphorous oxyhalide" or "phosphorous oxide." *See* claim 1, element (b). In contrast, VILLA does not mention phosphorous oxyhalide nor phosphorous oxide. To the contrary, the reference mentions no use of phosphorous at all.

11. The treatment of citalopram with phosphorous oxychloride ($POCl_3$) removes two impurities, namely the carboxamide impurity and the desmethyl impurity. Our process converts the carboxamide impurity into the desired end-product. This is a significant advantage over the VILLA process, because our invention increase both purity and yield.

12. Our claimed invention works better than when the cyanide exchange reaction is carried out as per the teachings of VILLA in absence of added iodide. I provide evidence of this in the Specification. Tables II and III show that citalopram of about 70-78% purity is obtainable when the reaction is carried out in absence of added iodide, as per VILLA. In contrast, our Examples 1 to 5 demonstrate preparation of citalopram of improved purity when the cyanide exchange reaction is carried out in presence of an iodide. Pointedly, our examples provide data showing preparation of citalopram of purity > 94%.

13. Our results would not have been expected by one of skill in the art. One of skill in the art would not read VILLA nor PETERSEN to suggest this result. There is a nexus between this evidence and the pending patent claims, because this evidence would be considered by one of skill in the art to have probative value in showing the pending patent claims are non-obvious in light of the art of record.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United State Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon or any patent to which this verified statement is directed.

Thennati RAJAMANNAR, Ph.D.
Dated as of Friday, August 5, 2005

Enclosure : *curriculum vitae*

SD:\Sun\10.500,532 Declaration (July 2005).doc

Curriculum Vitae

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Date of Birth	:	22.07.1961
Nationality	:	Indian
Sex	:	Male

Academic Qualifications:

Degree	Subject	Name of University	Remarks
M. Sc.	Chemistry (1981-83)	University of Madras	Outstanding
Ph. D.	Organic Chemistry (1983-88)	IIT, Madras	Radical mediated Annulations
Post Doctoral Work	Carbohydrate Chemistry (Organic Chem.) (1988-90) with Prof. A Vasella	University of Zürich, Switzerland	Synthesis and Chemistry of Anomeric Carbenes.

Experience:

Designation/Specialization	Organization
Scientist - Organic Chemistry (1990 - 93)	SPIC Science Foundation, Chennai, India. ➢ Synthetic pheromones ➢ Plant growth regulators ➢ New Synthetic methodologies
1993 - till date with Sun Pharma Advanced Research Centre. Currently heading Research Activities	Sun Pharma Advanced Research Centre, Baroda. Process: ➢ Processes for more than 100 API's ➢ Novel synthetic routes ➢ Polymorphs. Medicinal Chemistry: ➢ Allergy ➢ Inflammation ➢ Immunology

Publications:

13 Publications in international Journals

Patents filed more than 70.